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EUROPEAN PATENT SPECIFICATION(45) Date of publication of patent specification: **13.04.94** (51) Int. Cl.⁵: **C07D 333/28**(21) Application number: **88201494.7**(22) Date of filing: **12.07.88**(54) **Process for preparing thiophene derivatives.**(30) Priority: **14.07.87 GB 8716587**(43) Date of publication of application:
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**JOURNAL OF ORGANIC CHEMISTRY, Vol. 36,
No. 18, 1971, pages 2690-2692 Easton, PA, US;
M.G. REINECKE et al.: "The Reactions of
Halothiophenes with Metal Amides. A Con-
venient Preparation of beta-
Bromothiophenes"**

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Description

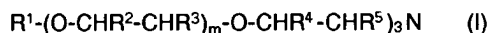
The present invention relates to a process for the preparation of certain beta-substituted thiophene derivatives from the corresponding beta-unsubstituted thiophenes.

The conversion of 2-halo thiophenes into 3-halo thiophenes is known from EP-A-0166182. In this document the conversion of 2-bromo and 2-chloro thiophene into 3-bromo and 3-chloro thiophene has been described using a zeolithe catalyst. The starting material, together with a large amount of benzene, were contacted with a ZSM-5 zeolithe catalyst in the H-form at a temperature between 200 and 250 °C. Conversions of about 80% were obtained.

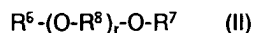
Reinecke M.G. et al, J. Org Chem., Vol 36, No. 18, 1971, pages 2690 to 2692 describe a process for the preparation of certain beta-bromothiophenes from alpha-bromothiophenes using sodium or potassium amide in liquid ammonia. While the process works well on a laboratory scale, it would be extremely difficult to perform on a commercial scale because of the difficulty of handling liquid ammonia.

Surprisingly we have now found an advantageous process for the preparation of certain beta-bromothiophenes which does not require liquid ammonia.

Accordingly, the present invention provides a process for the preparation of a thiophene derivative which is substituted at the beta-position by a bromine atom, which comprises reacting the corresponding beta-unsubstituted thiophene with an aromatic compound which is substituted with a bromine atom, in the presence of an alkali metal amide and a catalyst selected from one or more compounds of general formula



in which R^2 , R^3 , R^4 and R^5 are independently selected from a hydrogen atom and an alkyl group having up to 4 carbon atoms; R^1 represents an alkyl, cycloalkyl, phenyl, alkylphenyl or phenylalkyl group in which any alkyl or cycloalkyl group has up to 12 carbon atoms; and m is 0 or an integer from 1 to 10; or from one or more compounds of general formula



in which R^6 and R^7 , which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms; in each $O-R^8$ unit, which may be the same or different, R^8 independently represents a group selected from CHR^9CHR^{10} and $CHR^9CHR^{10}CR^{11}R^{12}$

in which R^9 , R^{10} , R^{11} and R^{12} are independently selected from a hydrogen atom and alkyl group having from 1 to 4 carbon atoms; and r represents an integer of from 1 to 15.

The aromatic compound is preferably a thiophene derivative, for example 2-bromothiophene, 2,5-dibromothiophene, 2,3,5-tribromothiophene or 2,3,4,5-tetrabromothiophene. The use of 2-bromothiophene or 2,5-dibromothiophene is preferred. However the aromatic compound can be other than a thiophene, such as a polybromobenzene; e.g. a tetrabromobenzene, a pentabromobenzene or hexabromobenzene.

It will be appreciated that mixtures of aromatic compounds may be used. This may be particularly advantageous when the process used to prepare the aromatic compounds affords them in such a mixture, since a separation step is then not needed.

The beta-unsubstituted thiophene may be unsubstituted or substituted by one or more substituents which do not take part in the reaction, for example by a halogen atom such as a chlorine or bromine atom, an alkyl group such as a methyl group, or a nitrile group. Alternatively the thiophene portion of the beta-unsubstituted thiophene may be fused to another aromatic ring, for example as in benzo[b]thiophene. Preferably the beta-unsubstituted thiophene is thiophene itself.

In some cases, the beta-unsubstituted thiophene and the aromatic compound may be the same compound.

It will be appreciated that when both beta-positions of the beta-unsubstituted thiophene are unsubstituted, then it is possible to obtain a product which is mono- or disubstituted at the beta position. For example, 3-bromothiophene can be obtained by reacting an excess of thiophene with an alpha-bromothiophene such as 2-bromothiophene or 2,5-dibromothiophene, for example using from 3 to 7 moles of thiophene per mole of alpha-bromothiophene, and 3,4-dibromothiophene may be prepared by reacting 2,5-dibromothiophene with itself.

The alkali metal amide employed in the process according to the invention may be, for example, a sodium or potassium amide. The amount of alkali metal amide employed in the process is not critical, but is preferably in the range of from 0.5 to 5 moles per mole of migrating substituent, more preferably from 1.5 to 3 moles.

The compounds of formulae (I) and (II) are known. A suitable catalyst of the formula II is ethylene glycol.

Preferably, the catalyst is tris(3,6-dioxaheptyl)-amine or tris(3,6-dioxaoctyl)amine.

The amount of catalyst employed in the process according to the invention will depend upon the chosen reaction conditions and the particular catalyst which has been selected. Generally the amounts will be in the range of from 0.5 to 5 grammes per mole of migrating substituent, preferably 0.75 to 1.5 grammes per mole.

The process according to the invention may conveniently be effected at a temperature in the range of from 10 to 90°C, preferably from 40 to 70°C. It will be appreciated that the process described by Reinecke M.G. et al, J. Org Chem., Vol 36; No. 18, 1971, pages 2690 to 2692 requires very low temperatures. Thus it is particularly advantageous that the process according to the invention may be performed at a temperature in the range of from 10 to 90°C. Conveniently the process is effected under an inert atmosphere such as nitrogen gas.

The process may, if desired, be effected in the presence of an inert solvent. However, it is preferable to effect the process in the presence of an excess of the beta-unsubstituted thiophene; for example the molar ratio of beta-unsubstituted thiophene to aromatic compound may be in the range of from 1:1 to 25:1, preferably from 5:1 to 15:1.

Suitable inert solvents which may be employed in the process according to the invention include ethers; e.g. tetrahydrofuran, dioxan or diethyl ether, and aromatic hydrocarbons; e.g. toluene. Toluene is preferred when a solvent is used.

The work up of reaction mixtures may be effected by standard methods of organic chemistry, e.g., quenching, then solvent extraction or steam distillation followed by fractional distillation.

The beta-substituted thiophene derivatives preparable by the process according to the invention are useful as intermediates in the preparation of pharmaceutical compounds. For example, 3-bromothiophene may be used to prepare 3-thienyllithium which may itself be used to prepare the vasodilator, Tinofedrine as described in Drugs of the Future, 1979, Vol 4, 286-290. 3,4-Dibromothiophene may be used in the preparation of conducting polymers, as described by G. Tourillon and F. Garnier in J. Electro. Anal. Chem; 1984, vol 161, part 1, pages 51 to 58. 3-Bromo-4-methylthiophene is useful in the preparation of pharmaceuticals, as described in European patent application EP 53603.

The following Examples illustrate the invention.

Example 1

Preparation of 3-bromothiophene using 2,5-dibromothiophene

2,5-Dibromothiophene (24.2 g, 0.1 mole), tris (3,6-dioxaheptyl) amine (0.1 g, 0.0003 mole), thiophene (60 cm³) and sodium amide (23.4 g, 0.6 mole) were successively charged to a 250cm³ three-necked round bottomed flask which had previously been purged with dry nitrogen gas for 1 hour. The reaction mixture was stirred and heated under nitrogen at 50-60°C for 4 hours. The reaction mixture was quenched with butan-1-ol and then water. The organic layer was separated and the aqueous layer extracted with dichloromethane. The organic layer, after dichloromethane and thiophene removal by distillation, yielded 28.4 g of product. Analysis of the product by gas chromatography with internal standard showed the sample to be mainly mono-bromo thiophenes in the ratio 2 parts 2-bromothiophene to 98 parts 3-bromothiophene.

3-Bromothiophene has the following physical characteristics:

Boiling Point 95°C at 100 mm Hg

¹H nmr (CCl₄, TMS)

δ/ppm: 6.91-7.20 (m, H2, H4, H5).

Example 2

Preparation of 3-bromothiophene using 2-bromothiophene

2-Bromothiophene (16.3 g, 0.1 mole), tris (3,6-dioxaheptyl)amine (0.1 g, 0.0003 mole), thiophene (50 cm³) and sodium amide (7.8 g, 0.2 mole) were successively charged to a 250 cm³ three-necked round bottomed flask which had previously been purged with dry nitrogen gas for 1 hour. The reaction mixture was stirred and heated under nitrogen at 50-60°C for 12 hours. The reaction mixture was quenched with butan-1-ol and then water. The organic layer, after dichloromethane and thiophene removal, yielded 19.4 g of product. Analysis of the product by gas chromatography with internal standard showed the sample to be mainly monobromothiophenes in the ratio 3 parts 2-bromothiophene to 97 parts 3-bromothiophene.

Example 3

Preparation of 3-bromothiophene using 2,5-dibromothiophene

Sodium amide (11.7g, 0.3 mole) and thiophene (100cm³) were charged to a 250cm³ three-necked round bottomed flask which had previously been

purged with dry nitrogen gas for 1 hour.

2,5-dibromothiophene (24.2g, 0.1 mole) and tris (3,6-dioxaheptyl) amine (0.1g, 0.0003 mole) were added over 5-10 minutes. The reaction mixture was stirred and heated under nitrogen at 50-60 °C for 6 hours.

After cooling to 25 °C methanol (14g, 0.4375 mole) was added over 1 hour to quench the sodium amide. Water (50cm³) was added and the organic layer steam distilled out. The organic layer was separated from the water and analysed by gas chromatography. The product (113.9g) was found to contain 22.7% 3-bromothiophene and 0.8% 2-bromothiophene, the remainder being thiophene and methanol, this is equivalent to a yield of 79% to 3-bromothiophene.

Example 4

Preparation of 3-bromothiophene using 2,5-dibromothiophene

2,5-Dibromothiophene (121g, 0.5 moles), tris (3,6-dioxaheptyl) amine (1.0g, 0.003 mole), thiophene (500 cm³) and sodium amide (58.5g, 1.5 mole) were successively charged to a flask which had previously been purged with nitrogen. The reaction mixture was stirred and heated under nitrogen at 50-60 °C for 6 hours. The product, after work up as described in Example 3, was found to contain 138.5g 3-bromothiophene and 2.6g 2-bromothiophene. The yield of 3-bromothiophene was 85% and the monobromothiophenes were in the ratio of 2 parts 2-bromothiophene to 98 parts 3-bromothiophene.

Example 5

Preparation of 3-bromothiophene using 2,3,5-tribromothiophene

2,3,5-tribromothiophene (21.2g, 0.07 moles), tris (3,6-dioxaheptyl) amine (0.2g, 0.0006 mole), thiophene (120 cm³) and sodium amide (11.7g, 0.3 mole) were successively charged to a flask which had previously been purged with nitrogen. The reaction mixture was stirred and heated under nitrogen at 50-60 °C for 6 hours. The product, after work up as described in Example 3, was found to contain 20.4g 3-bromothiophene and 0.8g 2-bromothiophene. The yield of 3-bromothiophene was 63% and the monobromothiophenes were in the ratio of 4 parts 2-bromothiophene to 96 parts 3-bromothiophene.

Example 6

Preparation of 3-bromothiophene using 2,3,4,5-tetrabromothiophene

2,3,4,5-tetrabromothiophene (20g, 0.05 moles), tris (3,6-dioxaheptyl) amine (0.2g, 0.0006 mole), thiophene (140 cm³) and sodium amide (11.7g, 0.3 mole) were successively charged to a flask which had previously been purged with nitrogen. The reaction mixture was stirred and heated under nitrogen at 50-60 °C for 6 hours. The product, after work up as described in Example 3, was found to contain 24.6g 3-bromothiophene and 0.8g 2-bromothiophene. The yield of 3-bromothiophene was 75% and the monobromothiophenes were in the ratio of 3 parts 2-bromothiophene to 97 parts 3-bromothiophene.

Example 7

Preparation of 3-bromo-4-methylthiophene using 2,5-dibromo-3-methylthiophene

2,5-dibromo-3-methylthiophene (25.6g, 0.1 mole), tris (3,6-dioxaheptyl) amine (0.2g, 0.0006 mole), 3-methylthiophene (100cm³) and sodium amide (11.7g, 0.3 mole) were successively charged to a flask which had previously been purged with nitrogen. The reaction mixture was stirred and heated under nitrogen at 50-60 °C for 6 hours. The product, after work up as described in Example 3 was found to contain 14.2g 3-bromo-4-methylthiophene, a yield of 43%.

3-Bromo-4-methylthiophene has the following physical characteristics:

boiling point 114 °C at 100 mm Hg

¹H nmr (CCl₄, TMS) δ/ppm: 7.12, 7.06 (d, H₂, J=2HZ), 6.86(m, H₅), 2.10 (s, CH₃).

Example 8

Preparation of 3-bromothiophene using ethylene glycol as catalyst

2,5-dibromothiophene (24.2g, 0.1 mole), ethylene glycol (0.5g, 0.008 mole), thiophene (100 cm³) and sodium amide (11.7g, 0.3 mole) were successively charged to a flask which had previously been purged with nitrogen. The reaction mixture was stirred and heated under nitrogen at 50-60 °C for 6 hours. The product, after work up as described in Example 3, was found to contain 9.1g 3-bromothiophene and 16g 2-bromothiophene. The yield of 3-bromothiophene was 29% and the monobromothiophenes were in the ratio of 64 parts 2-bromothiophene to 36 parts 3-bromothiophene.

Example 9Preparation of 3-bromothiophene using toluene as a solvent

2,5-Dibromothiophene (24.2g, 0.1 mole), tris (3,6-dioxoheptyl) amine (0.2g, 0.0006 mole), toluene (90cm³), thiophene (9.5cm³) and sodium amide (11.7g, 0.3 mole) were successively charged to a flask which had previously been purged with nitrogen. The reaction mixture was stirred and heated at 50-60°C under nitrogen for 6 hours. The product was found to contain 13.3g 3-bromothiophene and 0.9g 2-bromothiophene. The yield of 3-bromothiophene was 41% and the monobromothiophenes were in the ratio of 7 parts 2-bromothiophene to 93 parts 3-bromothiophene. Work up was effected by the addition of water and methanol, followed by filtration. The filtrate separated into two layers; the organic layer containing the title compound.

Example 10Preparation of 3,4-dibromothiophene using 3-bromothiophene

2,5-Dibromothiophene (24.2g, 0.1 mole), tris (3,6-dioxoheptyl) amine (0.2g, 0.0006 mole), 3-bromothiophene (100cm³) and sodium amide (11.7g, 0.3 mole) were successively charged to a flask which had previously been purged with nitrogen. The reaction mixture was stirred and heated at 50-60°C under nitrogen for 6 hours. The product, after work up as described in Example 3, was found to contain 25.5g 3,4-dibromothiophene, an apparent yield of 105% based on the 2,5-dibromothiophene.

3,4-Dibromothiophene has the following physical characteristics:

boiling point 111°C at 20mm Hg

¹H nmr (CCl₄, TMS) δ/ppm: 7.17 (s, H2 and H5)

Example 11Preparation of 3,4-dibromothiophene using tetrahydrofuran as solvent

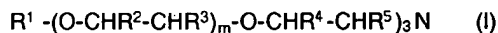
2,5-Dibromothiophene (24.2g, 0.1 mole), tris (3,6-dioxoheptyl) amine (0.1g, 0.0003 mole), tetrahydrofuran (100cm³) and sodium amide (11.7g, 0.3 mole) were successively charged to a flask which had previously been purged with nitrogen. The reaction mixture was stirred and heated at 50-60°C under nitrogen for 2 hours. The product, after work up as described in Example 3, was found to contain 3.3g of 3,4-dibromothiophene, a yield of 13%.

Example 12Preparation of 3-bromothiophene using hexabromobenzene

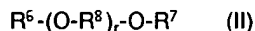
Hexabromobenzene (9.1g 0.017 mole), tris (3,6-dioxoheptyl) amine (0.1g, 0.0003 mole), thiophene (100cm³) and sodium amide (11.7g, 0.3 mole) were successively charged to a flask which had previously been purged with nitrogen. The mixture was stirred and heated under nitrogen at 50-60°C for 6 hours. The product, after work up as described in Example 3, was found to contain 0.47g 3-bromothiophene and 0.06g 2-bromothiophene. The yield on the assumption that one bromine only of the hexabromobenzene is utilised is 17% and the monobromothiophenes were in the ratio of 11 parts 2-bromothiophene to 89 parts 3 bromothiophene.

Claims

1. A process for the preparation of a thiophene derivative which is substituted at the beta-position by a bromine atom, which comprises reacting the corresponding beta-unsubstituted thiophene with an aromatic compound which is substituted with a bromine atom, in the presence of an alkali metal amide and a catalyst selected from one or more compounds of general formula



in which R², R³, R⁴ and R⁵ are independently selected from a hydrogen atom and an alkyl group having up to 4 carbon atoms; R¹ represents an alkyl, cycloalkyl, phenyl, alkylphenyl or phenylalkyl group in which any alkyl or cycloalkyl group has up to 12 carbon atoms; and m is 0 or an integer from 1 to 10; or from one or more compounds of general formula

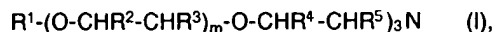


in which R⁶ and R⁷, which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms; in each O-R⁸ unit, which may be the same or different, R⁸ independently represents a group selected from CHR⁹CHR¹⁰ and CHR⁹CHR¹⁰CR¹¹R¹² in which R⁹, R¹⁰, R¹¹ and R¹² are independently selected from a hydrogen atom and alkyl group having from 1 to 4 carbon atoms; and r represents an integer of from 1 to 15.

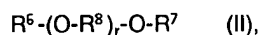
2. A process as claimed in claim 1, in which the aromatic compound is a thiophene derivative.
3. A process as claimed in claim 2, in which the aromatic compound is 2-bromothiophene or 2,5-dibromothiophene.
4. A process as claimed in any one of claims 1 to 3, in which the beta-unsubstituted thiophene is thiophene.
5. A process as claimed in any one of claims 1 to 3, in which the beta-unsubstituted thiophene and the aromatic compound are the same compound.
6. A process as claimed in any one of claims 1 to 5, in which the alkali metal amide is a sodium or potassium amide.
7. A process as claimed in any one of claims 1 to 6, in which the catalyst is tris (3,6-dioxaheptyl)-amine.
8. A process as claimed in any one of claims 1 to 7, in which the molar ratio of beta-unsubstituted thiophene to aromatic compound is in the range of from 1:1 to 25:1.
9. A process as claimed in any one of claims 1 to 8, in which the temperature is in the range of from 40 to 70 °C.

Patentansprüche

1. Verfahren zur Herstellung eines Thiophenderivats, das in der beta-Position durch ein Bromatom substituiert ist, welches ein Umsetzen des entsprechenden beta-unsubstituierten Thiophens mit einer aromatischen Verbindung, die mit einem Bromatom substituiert ist, in Gegenwart eines Alkalimetallamids und eines Katalysators, ausgewählt unter einer oder mehreren Verbindungen mit der allgemeinen Formel



worin R^2 , R^3 , R^4 und R^5 unabhängig voneinander unter einem Wasserstoffatom und einer Alkylgruppe mit bis zu 4 Kohlenstoffatomen ausgewählt sind; R^1 eine Alkyl-, Cycloalkyl-, Phenyl-, Alkylphenyl- oder Phenylalkylgruppe darstellt, worin eine Alkyl- oder Cycloalkylgruppe bis zu 12 Kohlenstoffatome aufweist; und m den Wert 0 hat oder eine ganze Zahl von 1 bis 10 bedeutet; oder unter einer oder mehreren Verbindungen mit der allgemeinen Formel



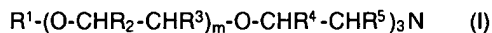
worin R^6 und R^7 , die gleich oder verschieden sein können, jeweils ein Wasserstoffatom oder eine Alkylgruppe mit 1 bis 4 Kohlenstoffatomen bedeuten; in jeder Einheit $O-R^8$, die gleich oder verschieden sein kann, R^8 unabhängig eine unter CHR^9CHR^{10} und $CHR^9CHR^{10}CR^{11}R^{12}$ ausgewählte Gruppe bedeutet, worin R^9 , R^{10} , R^{11} und R^{12} unabhängig voneinander unter einem Wasserstoffatom und einer Alkylgruppe mit 1 bis 4 Kohlenstoffatomen ausgewählt sind; und r eine ganze Zahl von 1 bis 15 bedeutet, umfaßt.

2. Verfahren nach Anspruch 1, worin die aromatische Verbindung ein Thiophenderivat ist.
3. Verfahren nach Anspruch 2, worin die aromatische Verbindung 2-Bromthiophen oder 2,5-Dibromthiophen ist.
4. Verfahren nach einem der Ansprüche 1 bis 3, worin das beta-unsubstituierte Thiophen Thiophen ist.
5. Verfahren nach einem der Ansprüche 1 bis 3, worin das beta-unsubstituierte Thiophen und die aromatische Verbindung die gleiche Verbindung sind.
6. Verfahren nach einem der Ansprüche 1 bis 5, worin das Alkalimetallamid ein Natrium- oder Kaliumamid ist.
7. Verfahren nach einem der Ansprüche 1 bis 6, worin der Katalysator Tris(3,6-dioxaheptyl)amin ist.
8. Verfahren nach einem der Ansprüche 1 bis 7, worin das Molverhältnis von beta-unsubstituiertem Thiophen zu aromatischer Verbindung im Bereich von 1:1 bis 25:1 liegt.
9. Verfahren nach einem der Ansprüche 1 bis 8, worin die Temperatur im Bereich von 40 bis 70 °C liegt.

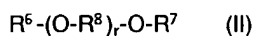
Revendications

1. Un procédé pour la préparation d'un dérivé de thiophène qui est substitué en position bêta, par un atome de brome, procédé selon lequel on fait réagir le thiophène bêta-non substitué correspondant avec un composé aromatique qui est substitué par un atome de brome, en présence d'un anidure de métal alcalin et d'un

catalyseur choisi parmi un ou plus d'un des composés de la formule générale



dans laquelle R^2 , R^3 , R^4 et R^5 sont choisis indépendamment parmi un atome d'hydrogène et un groupe alkyle ayant jusqu'à 4 atomes de carbone ; R^1 représente un groupe alkyle, cycloalkyle, phényle, alkylphényle ou phénylalkyle dans lequel un groupe alkyle ou cycloalkyle quelconque a jusqu'à 12 atomes de carbone ; et m est 0 ou un nombre entier de 1 à 10 ; ou de un ou de plus d'un composé de la formule générale :



dans laquelle R^6 et R^7 , qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un groupe alkyle ayant de 1 à 4 atomes de carbone ; dans chaque motif $O-R^8$, ces motifs pouvant être différents, R^8 représente indépendamment un groupe choisi parmi CHR^9CHR^{10} et $CHR^9CHR^{10}CR^{11}R^{12}$ dans lesquels R^9 , R^{10} , R^{11} et R^{12} sont choisis, de façon indépendante, parmi un atome d'hydrogène et un groupe alkyle ayant de 1 à 4 atomes de carbone ; et r représente un nombre entier de 1 à 15.

lequel le catalyseur est la tris(3,6-dioxaheptyl)-amine.

- 5 8. Un procédé tel que revendiqué dans l'une quelconque des revendications 1 à 7, dans lequel le rapport molaire du thiophène non-substitué en position bêta au composé aromatique se situe dans la gamme de 1:1 à 25:1.
- 10 9. Un procédé tel que revendiqué dans l'une quelconque des revendications 1 à 8, dans lequel la température se situe dans la gamme de 40 à 70 °C.
- 15
- 20
- 25
- 30
- 35 2. Un procédé tel que revendiqué dans la revendication 1, dans lequel le composé aromatique est un dérivé du thiophène.
- 40 3. Un procédé tel que revendiqué dans la revendication 2, dans lequel le composé aromatique est le 2-bromothiophène ou le 2,5-dibromothiophène.
- 45 4. Un procédé tel que revendiqué dans l'une quelconque des revendications 1 à 3, dans lequel le thiophène non-substitué en position bêta est le thiophène.
- 50 5. Un procédé tel que revendiqué dans l'une quelconque des revendications 1 à 3, dans lequel le thiophène non-substitué en position bêta et le composé aromatique sont le même composé.
- 55 6. Un procédé tel que revendiqué dans l'une quelconque des revendications 1 à 5, dans lequel l'amidure de métal alcalin est un amidure de sodium ou de potassium.
7. Un procédé tel que revendiqué dans l'une quelconque des revendications 1 à 6, dans